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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,699	05/08/2002	Dan L. Eaton	P3230R1C001-168	9949

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,699	EATON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,11-14 and 16-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6,11-14 and 16-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-19-05 has been entered.

The response, declaration and IDS filed 9-19-05 have been entered into the record. Claims 4-6, 11-14 and 16-31 are pending and under examination.

The text of Title 35 of the US Code can be found in the previous office action of record.

Rejections/Objections Withdrawn

The rejection of claims 4-6, 13, 14 and 26-31 under 35 USC 112, first paragraph as failing to comply with the enablement requirements for deposit is withdrawn in view of the new declaration (37 CFR 1.808) of record which has been properly executed.

Rejections/Objections Maintained

Priority

Applicants again argue their priority documents for date of invention. This is again not persuasive. Simply stated, a priority document, any priority document, for which Applicants claim priority under 35 USC 120 or 35 USC 119(e) must meet the requirements of 35 USC 112, first paragraph. None of the priority documents meet the requirement of 35 USC 112, first paragraph, including the instant application, for the plethora of reasons already made of record. The prior art date is the instant filing date of 5-8-02.

Claims 4-6, 11-14 and 16-31 stand rejected under 35 USC 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility is maintained for reasons made of record.

Applicants' arguments are again not persuasive for all the reasons made of record and again reiterated herein. Applicants again review the legal standard. This is again not persuasive and has been addressed previously Applicants' arguments in regard to the rejections of record are not persuasive and are briefly reiterated herein. Applicants argue that the PTO has not established a prima facie case for lack of utility. Applicants again argue the legal standard. Applicants argue that the requirement for a substantial utility defines a "real world use" and cite *Brenner v Manson*, 383 US 519,534(1996) already of record. Applicants argue that MPEP 2107.01 that states that office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulation to mean that products or services based on the claimed invention must be "currently" available to the public. This is not persuasive, the rejection set forth did not require "current public availability", but a specific and substantial utility for the now claimed invention. Applicants argue that any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial utility". This is not persuasive, the relied upon utility (increased nucleic acid levels in tumors as compared to a universal control) specifically requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use and as such is therefore not a "substantial utility" (see MPEP 2107.01(1)). Applicants cite and rely upon *Nelon v Bowler* and *Cross v Iizuka* et al that address the issue of in vitro results. This is not persuasive; the issue addressed in these cases is the correlation of in vitro results with in vivo activity, a question that is not at issue here. Each of the cases addresses pharmacological activity of the compound *in vitro* and its correlation with *in vivo* results. In the instant case the nucleic acid has not been demonstrated in any *in vitro* experiment to have any

pharmacological activity. The issue here is specific and substantial utility, not pharmacological activity and not the correlation of *in vitro* results with *in vivo* activity. A well-established utility must be specific, substantial and credible. Since, the utility does not meet either of the specific or substantial prongs of the utility assessment, credibility (i.e. the asserted unbelievably) was not assessed). Applicants assert that the utility on its face must be acceptable unless there is reason in the art to question the objective truth of the statement of utility or its scope. Applicants are directed to the plethora of reasons and evidence set forth in the first office action of record, for which the office relies upon to question the objective truth of the assertions in the specification. Applicants further argue that the USPTO must establish that it is more likely than not that one of skill the art would doubt the truth of the statement of utility, namely that the gene encoding the PRO is differentially expressed in certain cancers compared to normal tissue and useful as a diagnostic tool. The argument has been fully considered, but is not persuasive. Utility requires that the skilled artisan be able to use the claimed invention. Applicants argue that the nucleic acid is significantly overexpressed. As previously pointed out, there is no data regarding the reproducibility and statistical significance in any cancer as compared to the corresponding control and Applicants are attempting to rely upon a correlation of increased mRNA levels with increased protein levels. Applicants allege that the mRNA is significantly overexpressed and significantly different per the Declarations of Dr. Grimaldi. The examiner did not summarily dismiss opinions. In assessing the weight to be given expert testimony, the examiner may proper consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See *Ex parte Simpson*, 61 USPQ2d 1009 (BAPI 2001), *Cf Redac Int'l. Ltd. V. Lotsu Development Corp.*, 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), *Paragon Podiatry Lab., Inc. v. KLM Lab., Inc.* 948 F.2d 1182, 25 USPQ2d 1561, (Fed cir. 1993). In the instant case the fact sought to be

established is a statistical difference between mRNA levels in cancer versus normal controls. Dr. Grimaldi's declaration experimental parameters that are not set forth in the specification. The experimental parameters alleged by Dr. Grimaldi are not supported by way of written description in the specification as filed and one skilled in the art would have not been aware that the relied upon experimental parameters were the ones used to establish a different. Further, the mere visual difference of two different spots does not provide a difference in levels because it does not provide for normalization of total amount of mRNA. Declarant present not actual facts, but conclusion based on evidence not set forth before the examiner. The declaration of Dr. Grimaldi does not support the relative or absolute levels of the claimed nucleic acid was visually different and statistically significant across multiple samples. No evidence is proffered to support the conclusions reached by Declarant. Neither the specification, nor the declaration provides any evidence that indicates what the differences were or if they were statistically significant. Statistical relevance is requisite for a diagnostic for which Applicants rely. It is noted that the teachings of the specification support only "more highly expressed", a term of degree that does not establish statistical significance. No evidence is proffered by any Declaration to support statistical significance, relative or absolute levels. Applicants read into the specification that which they wish was there. The specification as filed is devoid of any explanation of number of samples tested, the variability and the statistical significance using art accepted parameters. What Applicants think is implied by the specification is irrelevant, when the means and methods and description do not provide for their conclusion. The description lacks description providing for indication of analysis of multiple independent samples and the population variation thereof and the methods of determining statistical significance using art established parameters. 1.1 is different from 1.0, is it statistically significant across a population? Applicants argue that evidence must be presented that doubts the credibility. As previously set forth, credibility was not assessed because the claimed invention did not meet the specific and substantial prong of

well-established utility. Applicants argue that the examiner must provide countervailing evidence. The examiner provided such evidence such as the teaching of Haynes et al. (Electrophoresis, 19:1862-1871, 1998) found "a general trend" but no significant correlation between nucleic acid level and translation and protein levels. Further, Haynes et al teach that polypeptide levels cannot be accurately predicted from mRNA levels and that variances as much as 40-fold or even 50-fold were not uncommon (p 1863). Haynes et al used yeast as an art-accepted model for eukaryotic systems. Additionally, Anderson et al., (Electrophoresis, Vol. 18, pages 533-537, 1997) and Chen et al., (Molecular and Cellular Proteomics, Vol. 1, pages 304-313, April 2002) also come the same conclusion in surveys of other tissues and cancers. Applicants argued that Dr. Polaris's declaration, which is devoid of any independently presented data, and relies upon conclusions based on data not set forth before the examiner, should be accepted. This is not persuasive, the examiner has presented Hun et al and Haynes et al to doubt the correlation between mRNA level and role in disease and the correlation of mRNA with protein production. Dr. Polaris's declaration does not speak to the claimed invention and is lacking data that can be independently assessed. As such, it is a mere conclusion is based on evidence not set forth before the examiner. Applicants again argue the Declaration of Dr. Ashkenazi. As previously set forth, the specification does not teach tumor classification for more accurate therapy as a contemplated utility and there is no teaching of how to perform such use. Applicants are attempting to rely upon a non-disclosed utility that is not well established for nucleic acids at the time of filing. Applicants argue that by virtue of their differential expression, the claimed polypeptides are useful as diagnostic tools regardless of whether or not the encoded polypeptides are also differentially expressed. Applicants have argued the encoded polypeptide has utility; the examiner disagrees for all the reasons made of record. However, since the claims no longer require that the nucleic acid encode a polypeptide or have expression vectors comprising such, the issue is moot.

With respect to a known role in cancer, this was provided in the first office action as a means for establishing a utility and is moot here.

The levels of mRNA have not been set forth by the specification as originally filed and therefore Haynes et al makes a significant point about the association of measured levels of mRNA with disease. Again it is noted that no absolute levels have been described and the fold-difference not described. As such, Haynes et al calls into question the factual findings reported in the specification described as "overexpression" or "more highly expressed". Haynes et al is very relevant because Applicants specification does not describe the mRNA levels and does not describe the protein levels and Applicants are attempting to rely upon the mRNA levels for an association with disease. Therefore, the rejection of record calls into question the findings as it relates to the alleged diagnosis of tumors/cancer in Example 18 of the specification. Haynes et al does not support the correlation between mRNA levels and protein expression. The quid pro quo of a US patent is that Applicants must place the invention in the public domain in a manner that allows the skilled artisan to practice the claimed invention. The fact that the skilled artisan would have to perform further experimentation to determine if the nucleic acid could perhaps be used indicates that the claimed invention does not meet the statutory requirements of well-established utility. Applicants argue that Example 18 provides for ample information regarding how to perform the assay and provides for "differential expression".. This is not persuasive for all the reasons of record. The means, method and alleged statistics used in Example 18 is obscure at best. No absolute value is not set forth at all. The normal is higher than the disease. The means for analysis is not set forth. What is the normalized ratio? No measurement of statistical assessment of the single point assay. The statistical significance "p value" is not set forth. Applicants again argue the Declaration of Dr. Smith indication that in a majority of cases, that the molecule is confirmed as being overexpressed in normal tissue. Again, the declaration is not persuasive for reasons made of record. The declaration and Applicants arguments do not address what the levels were

and the statistical relevance. Further, the conclusions are again based on solid experimental evidence, evidence not set forth before the examiner. Applicants argue that nowhere in the specification indicates the difference in the overexpression levels were small. Yet, the specification does not describe the differences in the levels of expression. Applicants have not set forth the absolute level of mRNA. Applicants argue that mere differential expression is sufficient to establish a specific and substantial diagnostic utility. This is not persuasive, in the absence of multiple samples, statistical analysis, the specification provides for, a best, a starting point for testing to see if the nucleic acid provides for diagnosis. It is noted in this case that the normal control is higher than the disease melanoma. As such, testing is required to ascertain that the "more highly expressed" normal mRNA can reproducibly differentiate cancer tissues across a population. Finally, Declarant attest that the samples of the specification were pooled samples and such pooled samples are more likely to show differences. Pooled samples are an average of the levels of all the samples combined and therefore wipes out any between sample variability. A high inter-sample variability, a key factor in a diagnostic utility, would not provide for statistically meaningful results. Therefore, Declarant attesting to the pooling the samples essentially wipes out intra-sample variability and fails to establish statistical significance for a diagnostic assay.

The rejection is maintained for all the reasons made of record.

Claims 4-6, 11-14 and 16-31 stand rejected under 35 USC 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for reasons made of record.

Claims 4-5, 12-14 and 16-31 stand rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time that the application was filed, had possession of the claimed invention is maintained for reasons made of record.

Applicants' arguments have been carefully considered but are not persuasive. Applicants again argue a complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure. This again is not persuasive. There is no known correlation between function and structure that is the art does not teach such. The art does not teach the function of the polypeptide. Therefore, Applicants are attempting to rely upon a disclosed correlation between structure and function. The underlying premise being similar structure predicting similar function is faulty. The function of the specie is in dispute and therefore any related compounds in dispute. The specification does not disclose hybridizing variants of the polynucleotide. Hybridization *per se* does not itself describe the primary structure of the hybridizing nucleic acid. Hybridization is a process step which in itself is a function defined under specific experimental conditions. Hybridizing nucleic acids do not have to encode the same or similar protein because hybridization does not define the reading frame of the polynucleotide. Therefore, mere hybridization does not and cannot define a similar polypeptide. Further, the specification as filed does not describe the isolation of any hybridizing nucleic acids with the claimed property. Similar hybridizing nucleic acid structure does not predict similar polypeptide function because minor changes to the nucleic acid can reflect large changes in the structure of the described encoded polypeptide. A single nucleotide insertion or deletion can change the reading frame and encode a completely different protein. The specification does not meet the conditions set forth in examples 9 or 10 of the Written Description Guidelines, because no hybridizing nucleic acids were obtained or described in

the instant specification. Either Applicants were in possession of a number of species to support the broad genus of hybridizing polynucleotides or they were not. In the instant case, the genus is very broad and is deliberately designed by Applicants in the specification to encompass sequences from other species, human variants and non-naturally occurring polynucleotides. Applicants have provided no description of these other contemplated sequences that fall within the large genus. Applicants' reliance on *In re Wallach* is misplaced. The decision does not address hybridizing variants or polypeptide variant but the genus of nucleic acids encoding the identical polypeptide. The issue is not listing the variety of nucleic acids encoding the same polypeptide, but a hybridizing nucleic acid that does not have to encode anything related to the polypeptide of SEQ IDNO:52. The facts of Wallach are completely different from this case as set forth above. Applicants argue make and test by the skilled artisan. This again is not the issue. The issue is possession of a representative number of species to adequately describe the claimed genus. Applicants have possession of but one polypeptide, and no description of others. Applicants have possession of but one nucleic acid and fragments thereof but have no description of variants. Applicants argue Example 14 of the written description guidelines. This is also not persuasive, the disclosed peptide is not an enzyme with known and disclosed members of the genus where the art has structurally and functionally characterized the family. The claimed family has not been characterized for the expression. The claimed nucleic acid family has not been characterized at all. Structure of a nucleic acid does not predict structure of a polypeptide because it can not and does not tell the reading frame. There are at least 6 reading frames for every nucleic acid, three forward and three reverse. Therefore, mere hybridizing can not predict encoding the same or different polypeptide. Hybridization tells you that it hybridizes under certain specifically defined experimental conditions and nothing more. It does not tell the skilled artisan the primary structure of the nucleic acid and certainly can not tell the skilled artisan the reading frame of the nucleic acid or the primary structure of the encoded

polypeptide. Therefore, nucleic acid hybridization can not structurally describe the genus of polypeptide variants that are claimed. Finally, to reiterate the specification does not demonstrate possession of any hybridizing nucleic acid variant with the claimed function, much less the encoded polypeptide. Nucleic acid hybridization can not be equated with polypeptide structure per se for the reasons set forth supra. As such, Applicants arguments are not persuasive.

Claims 4-6, 14 and 16-31 stand rejected under 35 USC 102(e) as being anticipated by Baker et al (WO 01/64888, published September 20, 2001 with priority to December 1, 2000) is maintained for reasons made of record.

Applicants again argue their priority date. This again is not persuasive for reasons already made of record.

Claims 4-6, 11-14 and 16-31 stand rejected under 35 USC 102(e) as being anticipated by Baker et al (US PreGrant Publication US2003/0027275) is maintained for reasons made of record.

Applicants again argue their priority date. This again is not persuasive for reasons already made of record.

Claims 4-6, 11-14 and 16-31 stand rejected under 35 USC 102(e) as being anticipated by Ashkenazi et al (WO 00/77037, published December 12, 1000) is maintained for reasons made of record.

Applicants again argue their priority date. This again is not persuasive for reasons already made of record.

Claims 14, 16, and 21-25 stand rejected under 35 USC 112, second paragraph, as bind indefinite for failing to particular point out and distinctly claim the subject matter which applicants regard as the invention.

Applicants argue that "about" is defined as the referenced nucleotide sequence plus or minus 10%. This is not persuasive, the term as argued defined provides for both an lower and upper limit. The claims provide for only a lower limit using "at least" therefore the metes and bound of the limits are still unclear because "at least" does not provide for an upper limit as argued. Therefore the combination of the two terms remains prima facie indefinite because neither the upper or lower limit are defined. The terms as argued are contradictory in regard to the definition of an upper limit because asserted definition of "about" argues an upper limit, which is in contrast to the open-ended term "at least" which implies no upper limit. Therefore, the skilled artisan would not be able to ascertain if they were infringing upon the claim or not.

Claims 14 and 21-25 stand rejected under 35 USC 102(b) as being clearly anticipated by Valenzuela et al (WO 99/55721, published November 4, 1999) is maintained for reasons made of record.

Applicants again argue their priority date. This again is not persuasive for reasons already made of record.

Status of the Claims

All claims stand rejected.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the

grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 7:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER